

In the Specification

Please substitute the following paragraph beginning on page 6, line 20, through to page 7, line 10:

As shown in the Examples, the applicants have discovered that growth factor independent leukemia cells have a constitutively activated STAT-like DNA-binding factor (DBF). The STAT-like DBF was found to be STAT5. It was also discovered that constitutive activation of STAT5 correlates with cell proliferation. Furthermore the applicants found that cell proliferation could be inhibited by blocking STAT5 transcription factor using a double-stranded oligonucleotide containing the STAT5 binding sequence AGATTTCTAGGAATTCAAATC (SEQ ID NO:1) or GCCTGATTTCCCCGAAATGACGGCA (SEQ ID NO:2) or GTATTTCCCAGAAAAGGAAC (SEQ ID NO:3), which contain the STAT5 consensus binding site TTCNNNGAA, in which "N" means any nucleotide. This oligonucleotide with the STAT5 binding sequence penetrates into cells and serves as a competitive inhibitor that binds to activated STAT5 in the cells. Oligonucleotide bound, activated STAT5 is not available to bind to endogenous DNA at STAT5 binding sites and therefore ~~can not function i.e.~~ cannot function, i.e., activate the transcription of various cellular genes. Inhibiting the synthesis of protein by this method can have many effects on cells. In the current invention the inhibition of STAT5 function in this manner, prevented cell proliferation and led to the death of human leukemic cells *in vitro*. Hence, the data is highly predictive of the present invention being effective against human malignant cells.

Please substitute the following paragraph beginning on page 20, line 10, through to page 21, line 8:

Preparation of nuclear extracts and gel mobility shift assays were performed according to methods described previously (Yu 1993 Mol Cell Biol 13:2011). Briefly, equal amounts of nuclear proteins (5-10 µg) for each sample were incubated for 30 minutes at 30°C with 10,000 dpm of [³²P]-labeled double-strand DNA fragment (IRF-1 GAS), which contains the interferon-γ activation site (GAS) that binds to interferon regulatory factor (IRF-1) (5'-GCCTGATTTCCCCGAAATGACGGCA) SEQ ID NO 2 (GORODETSKY 1988 GENE 66:87), which

contains an identical sequence to that of Bovine mammary gland factor element (MGFe), TTCCCCGAA SEQ ID NO 6. For competition assays, unlabeled FIRE, (5'-AGCGCCTCCCCGGCCGGGGAG) SEQ ID NO 7, interferon-stimulated response element (ISRE; 5'-GATCGGGAAAGGGAAACCGAAACTGAAGCC) SEQ ID NO 8, and sis-inducible element (SIE, 5'-AGCTTCATTTCCTGTAATCCCTAAGC) SEQ ID NO 9 also were used as potential DNA-protein binding competitors, by adding 50X molar excess of each unlabeled DNA fragment, along with the [³²P]-labeled IRF-1 GAS (SEQ ID NO. 2) oligonucleotide probe. Unlabeled MGFe (SEQ ID NO. 1) was used as a specific competitor for STAT5 binding to IRF-1 GAS (SEQ ID NO. 2). For gel mobility supershift assays, nuclear extracts were co-incubated with the indicated specific anti-STAT antibodies and the [³²P]-labeled oligonucleotide probes. The DNA-protein complexes and unbound probe were separated electrophoretically on 5% native polyacrylamide gels in 0.5 X TBE buffer (44.5 mM Tris, pH 8.0, 1 mM EDTA and 44.5 mM boric acid) for 3 hours at constant 140 volts. The gels were fixed and dried, and the DNA-protein complexes were visualized by autoradiography at ~~-70°C~~ -70°C with Kodak X-OMAT film and a DuPont Cranex lightning-plus intensifying screen.

Please substitute the following paragraph beginning on page 23, line 9:

Applicants analyzed STAT DNA-binding factor activation by gel electrophoretic mobility shift assays (EMSA) with a [³²P]-labeled oligonucleotide containing the IRF-1 GAS (SEQ ID NO. 2) consensus STAT binding site, as the probe. DNA-binding protein(s) were detected in the nuclear extracts from Dami/HEL and Meg-01 cells in the absence of cytokine exposure (Fig. 2). Addition of as much as 400 ng/ml of TPO or 40 ng/ml IL-3 does not have any further effect on the constitutive DNA-binding protein activity in these growth factor-independent cell lines (Fig. 2). Exposure of these cells to GM-CSF, IL-6, EPO or TNF- α also did not result in significant enhancing or inhibitory effects on the constitutive DNA-binding factor activity. In contrast, no STAT-like DNA-binding factor was detectable in untreated control cells.

Please substitute the following paragraph beginning on page 23, line 27, through to page 24, line 18:

Experiments were performed to identify the specific STAT protein activated in these megakaryocytic leukemic cell lines. First, using a set of oligonucleotides to attempt to inhibit competitively the binding of the STAT-like factor to [³²P]-labeled IRF-1 GAS (SEQ ID NO. 2). When Dami/HEL and Meg-01 nuclear extracts were co-incubated with the labeled MGFe probe (SEQ ID NO. 1) plus a 100-fold molar excess of unlabeled SIE (SEQ ID NO. 9) or IRF-1 GAS (SEQ ID NO. 2) (Fig 4) or FIRE (SEQ ID NO. 7) or ISRE (SEQ ID NO. 8) oligonucleotides, which do not contain TTCCCCGAA sequence, no competitive inhibition of the formation of DNA-protein complexes was observed. However, a 50-fold molar excess of the unlabeled MGFe (SEQ ID NO. 1), which contains the same TTCCCCGAA STAT-binding sequence as IRF-1 GAS (SEQ ID NO. 2), completely abolished the formation of the labeled DNA-protein complexes. Similar results were found with Meg-01.

When the nuclear extracts from TPO-treated Mo7c cells were incubated with [³²P]-labeled IRF-1 GAS (SEQ ID NO. 2) probe or the [³²P]-labeled probe plus a 50-fold molar excess of unlabeled FIRE (SEQ ID NO. 7), ISRE (SEQ ID NO. 8), SIE (SEQ ID NO. 9) or MGFe (SEQ ID NO. 1) oligonucleotides, the cytokine-induced DNA-binding factor in Mo7c cells had the same features as the constitutively activated STAT-like factor in Dami/HEL cells. Both of the factors are able to bind to the IRF-1 GAS (SEQ ID NO. 2) probe, and their binding activity could be abolished completely by unlabeled MGFe (SEQ ID NO. 1), but not by oligonucleotides that do not contain the TTCNNNGAA sequence.